Case Report

Advanced lung adenocarcinoma (LUAD) patient with EGFR mutations benefited from multiline combination targeted therapies after osimertinib (AZD9291) resistance: a case report

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Background: The resistance mechanisms to osimertinib encompass on-target molecular alterations, such as the well-known epidermal growth factor receptor (*EGFR*) C797S resistance mutation, and off-target molecular alterations, such as the high-frequency *MET* amplification, but there's no further clear-cut therapeutic option to date for these individuals yet. Here we reported a lung adenocarcinoma (LUAD) patient who progressed on osimertinib benefited from multiline combination target-therapy and obtained a long-term progression-free survival (PFS).

Case Description: A 70-year-old Chinese woman without a smoking history presented with stage IV advanced LUAD harboring *EGFR* 19del and then developed *EGFR* T790M mutation after 6-month treatment of gefitinib [a first-generation EGFR tyrosine kinase inhibitor (TKI)]. Osimertinib (a third-generation EGFR TKI) was immediately initiated, and the PFS was 11 months. After disease progression, next-generation sequencing (NGS) identified *MET* amplification, in addition to *EGFR* 19del. Combination therapy of osimertinib and cabozantinib (a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2)/capmatinib (a MET inhibitor) was administrated to the patient and the best overall response (OR) was stable disease (SD) with the PFS of 10 months. NGS detected the emergence of novel mutations *EGFR* S784Y and *EGFR* L799Q, together with *EGFR* C797S and all in cis with *EGFR* T790M, and retention of *EGFR* 19 del. The patient received pemetrexed (a chemotherapy drug) and bevacizumab (a VEGFR inhibitor) and achieved a partial response (PR). After 6 months of PFS, combination therapy of brigatinib (an inhibitor of ALK and EGFR) and cetuximab (an EGFR inhibitor) was initiated and the patient achieved a long-term PFS of 18 months and SD. Her overall survival (OS) was 51 months.

Conclusions: This case highlights the importance of NGS on repeated biopsy which could offer better treatment options.

Keywords: Lung adenocarcinoma (LUAD); osimertinib; *MET* amplification; brigatinib and cetuximab; case report

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Introduction

Osimertinib is a well-known third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that is highly selective for common *EGFR*-activating mutations as well as the *EGFR* T790M mutation in advanced non-small cell lung cancer (NSCLC) patients, but most patients will inevitably develop resistance. As previously reported (1), the resistance mechanisms to osimertinib encompass on-target molecular alterations, such as the well-known *EGFR* C797S resistance mutation, and off-target molecular alterations, such as the high-frequency *MET* amplification. Due to tumor heterogeneity, more

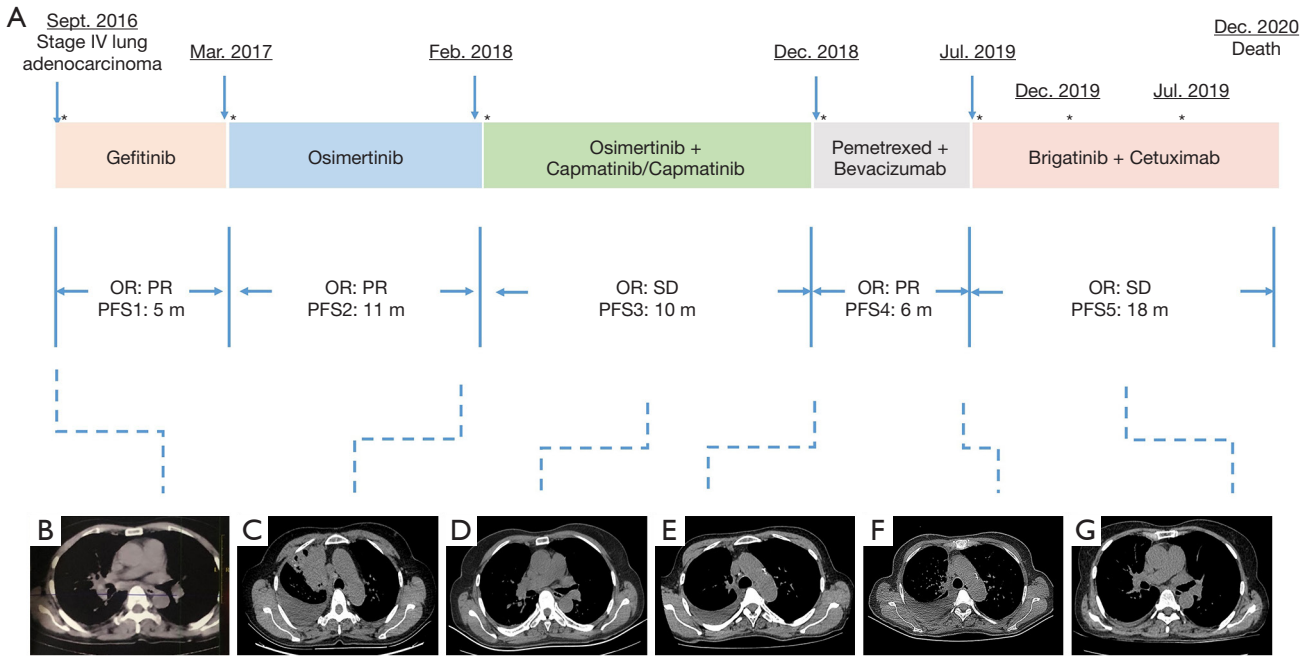


Figure 1 Timeline and clinical response of the patient's treatment. (A) Diagram illustrating the various treatments the patient received including PFS (in months) and the specific time points of next-generation sequencing performed on tissue and blood samples (indicated by asterisks). (B) PET scan before treatment. (C) CT imaging after 11 months of osimertinib treatment. (D) CT imaging after 7 months of combination treatment of osimertinib and cabozantinib/capmatinib. SD was achieved. (E) CT imaging after 10 months of combination treatment of osimertinib and cabozantinib/capmatinib. (F) CT imaging after 6 months of combination therapy of pemetrexed and bevacizumab. (G) CT imaging after 5 months of combination therapy of brigatinib and cetuximab. PR, partial response; OR, overall response; SD, stabled disease; PFS, progression-free survival; PET, positron emission tomography; CT, computed tomography.

novel resistance mechanisms were continually detected, including multiple resistance mutations (2). However, there's no further clear-cut therapeutic option to date for these individuals yet. In this study, we have reported an advanced Chinese lung adenocarcinoma (LUAD) patient who progressed on osimertinib benefited from multiline combination target-therapy and obtained a long-term PFS. We present the following article in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-510/rc).

Case presentation

A 70-year-old, female, never-smoker was referred to our clinic with a two-month history of persistent cough with sputum in September 2016. No past medical history was identified. Her father died of lung cancer, her mother died of intestinal cancer, her sister died of endometrial cancer. The treatment history and the images of the patient were shown in *Figure 1*. Positron emission tomography (PET) scan showed consolidation in the right upper lobe and multiple small pulmonary nodules in both lungs (*Figure 1B*). Transbronchial biopsy was performed on the right lung and histopathology confirmed moderate to poorly differentiated adenocarcinoma. Immunohistochemically, tumor cells in the main part were positive for CK7, TTF1, Napsin A, Ki 67 (40% +), and negative for p63, CD56, and Syn. According to the 8th edition of the tumor, node and metastasis (TNM) classification of lung cancer, this patient was classified as stage IV NSCLC.

Next-generation sequencing (NGS) identified *EGFR* exon 19 deletion (19 del) with the allele frequency (AF) 84.74%, and *EGFR* amplification at a copy number (CN) of 16.9. The first-generation EGFR TKI gefitinib was administered (*Figure 1A*, *Table 1*). At disease progression after 5 months' treatment, NGS analysis of broncho-fiberscope rebiopsy revealed *EGFR* T790M mutation, with the retention of 19 del. Osimertinib was immediately initiated at 80 mg daily, then added to 140 mg after 7 months. The best response was partial response (PR) and

Table 1 Table summarizing the mutations and their corresponding allele frequency (expressed in percentage) detected using next-generation sequencing of tissue, blood or hydrothorax samples at indicated time points

Gene	Mutation type	Sept. 2016 (tissue)	Mar. 2017 (tissue)	Aug. 2017 (blood)	Feb. 2018 (tissue & blood)	Dec. 2018 (tissue)	Jul. 2019 (tissue)	Dec. 2019 (hydrothorax)	Jul. 2020 (hydrothorax)
EGFR	E746_A750del	84.74%	72.73%	6.41%	9.2%	19.64%	15.09%	51.17%	38.52%
EGFR	T790M	ND	59.05%	ND	ND	23.01%	18.64%	57.36%	14.93%
EGFR	S784Y	ND	ND	ND	ND	9.72%	11.78%	4.28%	1.04%
EGFR	L799Q	ND	ND	ND	ND	9%	11.3%	3.87%	1.32%
EGFR	C797Sc.2390_2391delinsCT (in cis)	ND	ND	ND	ND	10.79%	6.21%	53.16%	13.64%
EGFR	C797S c.2389T>A (in cis)	ND	ND	ND	ND	ND	ND	ND	1.26%
TP53	c.782+1G>A	36.54%	38.57%	3.55%	5.06%	3.85%	1.75%	22.60%	6.17%
PIK3CA	E542K	ND	ND	ND	ND	ND	ND	1.48%	59.17%
CDK4	CN	ND	ND	ND	ND	ND	ND	3.6	5.0
EGFR	CN	16.9	ND	ND	ND	ND	ND	3.7	ND
MET	CN	ND	ND	ND	Amplification	ND	ND	ND	ND

ND, not detected.

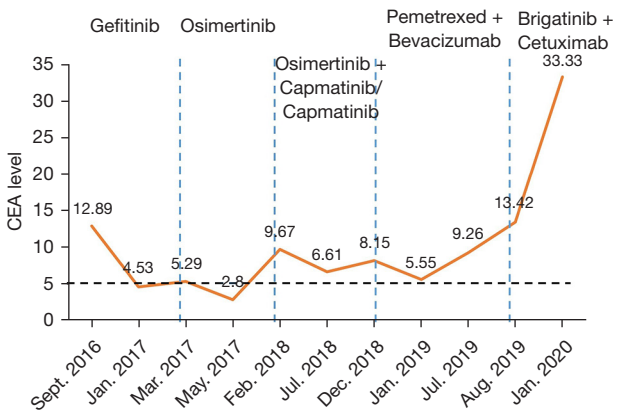
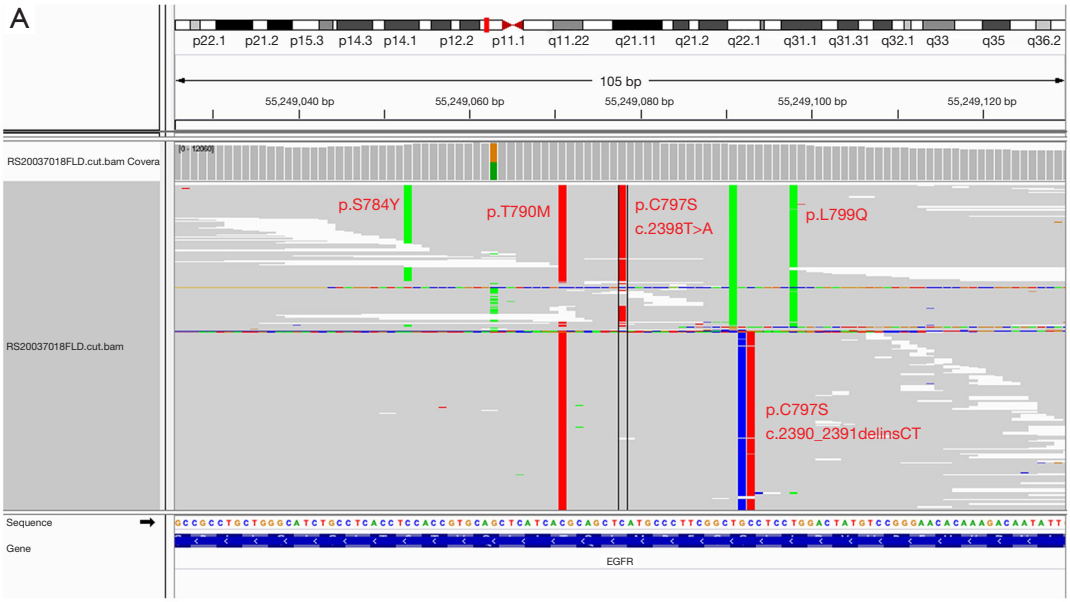


Figure 2 CEA levels during treatment. The normal range of CEA is 5 ng/mL (indicated by a dashed black line). CEA, carcinoembryonic antigen.

the serum level of blood tumor marker carcinoembryonic antigen (CEA) was significantly reduced after two months' treatment (*Figure 2*). After 11 months of progression-free survival (PFS), the patient experienced disease progression in her right upper lung lesion with pleural effusion (PE) (*Figure 1C*). Then, the blood and tissue-based NGS was performed and both detected *MET* amplification, in addition to *EGFR* exon 19 del in February 2018 (*Table 1*). Combination therapy of osimertinib (100 mg, bid) and cabozantinib (40 mg, bid) was administrated to the patient. Cabozantinib was switched to capmatinib (250 mg, bid) one month later due to the side effects of diarrhea and anorexia and increased CEA (*Figure 2*). Stabled disease (SD) was achieved and PFS was 10 months (Figure 1D). Pulmonary computed tomography (CT) revealed increase in lung nodules size and an increased volume of PE, with a new flake high-density shadow within the inferior lobe of the right lung in December 2018 (*Figure 1E*).

To screen for new treatment targets, NGS was performed on broncho-fiberscope rebiopsy samples in December 2018 and detected the emergence of acquired mutations *EGFR* S784Y (AF: 9.72%) and *EGFR* L799Q (AF: 9%), together with *EGFR* C797S c.2390_2391delinsCT (AF: 10.79%) and all *in cis* with *EGFR* T790M (AF: 23.01%), and retention of *EGFR* 19 del (AF: 19.64%). The patient received combination therapy of pemetrexed and bevacizumab, then observed a decrease in the primary lung mass two cycles later (from 27.5×28.5 to 22.5×26.5 mm). PR was achieved. After 6 months of PFS, follow-up CT scan demonstrated a wider septal thickening of the right lung, as well as an increase and partial enlargement of mediastinal and right hilar lymph nodes, indicating progressive disease (PD) (*Figure 1F*).

Tissue biopsy-based NGS was performed again in July 2019 and showed the same genetic alteration as before. Consequently, the patient received combination therapy of brigatinib (brigatinib initiated at 80 mg once daily for one week and increased by 40 mg/day every one week of treatment, and maintenance dose was 200 mg once daily)



B

EGFR	p.S784Y	p.T790M	p.C797s (c.2389T>A)	p.C797S (c.2390 2391delinsCT)	p.L790Q
p.S784Y	–	In cis	In cis		In cis
p.T790M	In cis	–	In cis	In cis	In cis
p.C797S (c.2389T>A)	In cis	In cis	–	In trans	In cis
p.C797S (c.2390_2391delinsCT)	In trans	In cis	In trans	–	In trans
p.L799Q	In cis	In cis	In cis	In trans	–

Figure 3 Next generation sequencing result of patient's hydrothorax in July 2020. (A) Sequencing reads of EGFR mutations visualized by the IGV. (B) Allelic context of different EGFR mutations. EGFR, epidermal growth factor receptor; IGV, Integrative Genomics Viewer.

and cetuximab (300 mg biweekly for the first 2 cycles, and maintenance dose was to 400 mg biweekly). She achieved a SD and the PFS was lasting 18 months with no adverse events other than mild fatigue transaminase elevation. During the treatment, she received molecular analysis on hydrothorax twice, five months later (Dec. 2019) and one year later (Jul. 2020) respectively (*Table 1*). The results were as below respectively: *EGFR* S784Y (AF: 4.28% *vs.* 1.04%), *EGFR* L799Q (AF: 3.87% *vs.* 1.32%), *EGFR* C797S (c.2390_2391delinsCT) (AF: 53.16% *vs.* 13.64%), *EGFR* C797S (c.2389T>A) (AF: 0 *vs.* 1.26%), *EGFR* T790M (AF: 57.36% *vs.* 14.93%), *EGFR* 19 del (AF: 51.17% *vs.* 38.52%). The S784Y, L799Q, and C797S (c.2389T>A) mutations exist *in trans* with C797S (c.2390_2391delinsCT) but all *in cis* with T790M (*Figure 3*). The patient died at the end of 2020, due to a heart problem, and her overall survival was 51 months.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

There is no effective care for heavily-treated and osimertinib-resistance metastatic LUAD patients yet, especially multiple resistance mutations (1). Multiple resistance mutations have been reported previously in very few cases similar to our patient, but no therapeutic regimen was reported, except for the idea of combination therapy (3). Here, we report an advanced LUAD patient with osimertinib-resistance who received subsequently combination targeted therapy and obtained a long-term

clinical benefit.

In our case, a *MET* amplification was initially detected after resistance to osimertinib. As previously reported, some preclinical or clinical studies have suggested that *MET* amplification is likely to be a key mechanism underlying acquired resistance to osimertinib (4,5). Combination therapy with EGFR-TKI and a MET inhibitor should be considered for these patients. However, most case reports or clinical studies were related to the combination therapy of first-generation EGFR-TKI and a MET inhibitor (5-8), and the effectiveness of treatments was variable. In this study, a combination therapy of osimertinib and cabozantinib/capmatinib was administrated to our patient, while only osimertinib plus capmatinib showed better effectiveness and tolerance, achieving SD with PFS of 10 months. The result suggested that combination therapy of osimertinib and capmatinib may be a potential choice for osimertinib-resistant patient with *MET* amplification.

We first reported the emergence of novel acquired mutations *EGFR* S784Y and L799Q, in addition to *EGFR* triple mutation (19 del/T790M/C797S) after progression on osimertinib plus capmatinib. *EGFR* S784F/P have been reported previously insensitive to gefitinib and erlotinib (9-12). Here, the S784Y and L799Q mutations exist *in trans* with C797S (c.2390_2391delinsCT) but all *in cis* with T790M, which indicated T790M plus *cis*-S784Y/L799Q may be a potential resistance mechanism to osimertinib.

A combination therapy of brigatinib and cetuximab, which potentially overcoming *EGFR* triple mutations (activating mutation, T790M, and *cis*-C797S) (13-15), was administrated to the patient and achieved a substantial clinical benefit with a PFS of 18 months. To our best knowledge, it's the first report that combined targeted therapy of brigatinib and cetuximab could be an effective treatment strategy to improve survival outcomes in patients who acquire *EGFR* 19 del-T790M-*cis*-C797S-S784Y-L799Q mediated resistance to osimertinib.

Taken together, the idea of combination therapy with EGFR-TKI and MET inhibitor for the patient harboring co-mutations of *MET* amplification and *EGFR* exon 19 del is feasible, and osimertinib plus capmatinib should be suggested as a potential effective choice. Also, the combination therapy of brigatinib and cetuximab may overcome the novel acquired *EGFR* (S784Y/L799Q/T790M) mutations, as well as *EGFR* triple mutations (activating mutation, T790M, and *cis*-C797S), but further study is needed.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-510/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-510/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-510/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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